Clinical trial of osteoarthritis jamu formula compare to piroxicam

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Abstrak

Latar belakang: *Indonesia memiliki beberapa ramuan tradisional yang telah digunakan untuk mengurangi nyeri pada osteoarthritis (OA). Namun belum ada bukti yang kuat mengenai khasiat dan keamanan dari ramuan tradisional. Penelitian ini memberikan bukti mengenai khasiat dan keamanan dari satu ramuan tradisional.*

Metode: *Penelitian ini menggunakan metode* randomized clinical trial *(RCT) dengan 123 subyek (pasien) selama 28 hari intervensi. Penelitian ini dilakukan pada bulan Maret – Desember 2014 oleh 30 dokter Saintifikasi Jamu di 20 provinsi. Formula jamu dibandingkan dengan piroksikam sebagai kontrol positif. Parameter yang digunakan untuk mengevaluasi khasiat formula jamu dan piroxicam adalah* visual analogue score (VAS)*,* pilot geriatric arthritis project (PGAP) functional status assessment *(FSA), dan* Short Form *(SF)-36. Untuk mengevaluasi keamanan digunakan nilai* serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase level (SGPT), blood urea nitrogen *(BUN), dan kreatinin.*

Hasil: *Sebanyak 123 pasien yang dibagi menjadi dua kelompok yaitu 63 subyek pada kelompok formula jamu dan 60 subyek pada kelompok piroksikam. Pemberian jamu dapat menurunkan VAS secara bermakna (p<0,05) jika dibandingkan dengan hari ke-0. Nilai FSA kelompok jamu turun secara bermakna (p=0,000) jika dibandingkan dengan nilai di awal intervensi. Formula jamu dapat memperbaiki nilai SF-36 bila dibandingkan dengan hari ke-0. Nilai ketiga parameter antara jamu formula dan piroksikam, jika dibandingkan tidak berbeda bermakna (p>0,05). Kelompok formula jamu menunjukkan nilai SGOT, SGPT, BUN, dan kreatinin dalam ambang normal.*

Kesimpulan: *Penelitian ini menunjukkan bahwa ramuan jamu secara klinis, khasiatnya sebanding dengan piroxicam dan aman setelah intervensi selama 28 hari.* ***(Health Science Journal of Indonesia 2016;7(2):84-92)***

Kata kunci: *khasiat, keamanan, RCT, ramuan*

Abstract

Background: Indonesian herbs have several formulas which have been used traditionally to reduce pain of osteoarthritis (OA). However, there is a lack of evidence of its efficacy and safety. The objectives of study were to investigate the efficacy and safety of a traditional formula for OA.

Methods: Design of the study was a randomized clinical trial (RCT) involved 123 patients (subjects) for 28 days intervention. This study was conducted between March - December 2014 with 30 physicians were participated at 20 regencies in Indonesia. The variables measured were VAS score, PGAP functional status assessment (FSA), and Short Form (SF-36) to assess jamu efficacy in comparison to piroxicam. To evaluate the safety of jamu formula using values of SGOT, SGPT, BUN, and creatinine.

Result: The jamu formula administration effects can reduce VAS significantly ($p<0.05$) if it was compared to baseline. FSA score of jamu formula group was decreased significantly ($p=0.000$) when compared to the start of intervention. Short Form (SF)-36 of jamu formula group were significantly improved when compared with baseline value. The result of the three parameters between jamu group and piroxicam group should not significantly different. There was no difference in those parameters between both groups ($p>0.05$). In biological parameters, SGPT, SGOT, BUN, and creatinine level, showed normal range in both groups.

Conclusion: This study showed that the efficacy and safety of jamu formula was clinically comparable to piroxicam after 28 days of treatment. ***(Health Science Journal of Indonesia 2016;7(2):84-92)***

Keywords: efficacy, safety, RCT, jamu formula

Steoarthritis (OA) results from an imbalance between breakdown, repair of the tissues in the synovial joint organ and occurs as a result of multiple risk factors including trauma, overuse, and genetic predisposition. It was estimated that 9.9 million adults had symptomatic osteoarthritis of the knee in 2010. Risk factors of the condition increase with age, especially in women. Genetics, large body mass, certain occupations, repetitive knee bending or heavy lifting, and hereditary vulnerability are other factors that increase one's risk of developing the disease.[1]

Some alternative therapy can be used to reduce OA. Neuromuscular electrical stimulation (NMES) is presented as a technique used by physical therapists,[2] and moderate pressure massage therapy can reduce pain and increase motion.[3] Yoga and tai chi showed significant reductions in pain caused by OA[4]. Hundreds of herbal remedies are used for treating OA and the research literature, it reflect only a small percentage of them. It seems that herbal remedies could effective to lower or stop the consumption of Nonstreroidal Antiinlammatory Drugs (NSAIDs) and to reduce the incidence of adverse effect of NSAIDs.[5]

Randomized controlled trial (RCT) of traditional herbal formulation administrated by topical from chamomile oil, can decrease pain and consumption of analgesic.[6] A lot of studies about oral herbal administrated are increasing and also interesting because it is compare with NSAIDs such as Chinese herbal recipes versus diclofenac. It shows that herbal recipes are as effective than conventional drug to reduce OA.[7] Previous study of jamu formula has been done before with pre post design and it shows jamu formula can decrease the joint pain.[8]

Indonesia has several herbs formulas which have been used traditionally to reduce pain of OA. The present study was conducted to investigate the efficacy and safety of traditional herbs formula that consist of *Curcuma xanthorrhiza* rhizome, *Centella asiatica* herbs, *Curcuma domestica* rhizome, *Foeniculum vulgare* seeds, *Orthosiphon stamineus* leaves, *Phyllantus niruri* herbs, *Equisetum debile* herbs. The efficacy of formula would be compared to piroxicam. The safety of formula would investigated by examined the kidney and heart function through evaluate the values of SGOT, SGPT, BUN, and creatinine.

METHODS

Plants and piroxicam materials

The formula were prepared by Post Harvest Section, Department of Research and Development Medicinal Plant and Traditional Medicine Center (B2P2TOOT) Tawangmangu Indonesia. The jamu was consisted of 15g *Curcuma xanthorrhiza* dried rhizome, 3g *Centella asiatica* dried herbs, 15g *Curcuma domestica* dried rhizome, 3g *Foeniculum vulgare* seeds, 5g *Orthosiphon stamineus* dried leaves, 7g *Phyllantus niruri* dried herbs, and 5g *Equisetum debile* dried herbs respectively.

Ten mg capsule of commercially marketed generic piroxicam were provided by PT. Indofarma (Indonesia). Subjects were selected randomly which use piroxicam, are presribed once daily 1 capsule, after meal.

Inclusion and exclusion criteria

Inclusion criteria of subject for this study were as follow: age within 50 – 70 years old, Visual Analogue Scale (VAS) that classified as medium or light cathegory with VAS 70 $\leq$VAS > 30 score, no history of allergic to herbal drugs, and did not take any other medication (analgesic, NSAIDs, etc) at least 2 weeks before intervention (washed out period). Exclusion criteria of subject included having complication diseases (subject's medical record), gastritic disorder, ulcus pepticus or ulcus duodenum, allergic of bitter herbs, hypersentitive of curcumin, and taking medication during the study.

Study design

This study was conducted at Medicinal Plant and Traditional Medicine Research and Development Center, Tawangmangu, Indonesia. The study designed was a prospective, randomize, open label, and multicenter to evaluate efficacy and safety of jamu formula that claims reduce pain of OA. The study was carried out between March - December 2014. Ethical clearance was approved by The Ethic Commission of Health Research and Development Department, Health Ministry Republic of Indonesia (LB.02.02/5.2/KE.148/2014).

Among 30 physicians and 123 patients were participated in this study. The physicians were from 20 regencies in Indonesia, who involved in Saintifikasi Jamu (SJ) program held by Ministry of Health Republic of Indonesia (Fig. 1). Prior to receive

treatment , all patient were checked on VAS score, PGAP functional status assessment (FSA), Short Form (SF-36), SGOT, SGPT, BUN, and creatinine. Every subject who had inclusion criteria, received form of compliance, and they should signed the form after they taken the jamu formula or piroxicam as well as when they forgot to take it.

Efficacy and safety measures

The efficacy of jamu formula was assessed as baseline, at days 7, 14, 21, 28. These assessments consist of VAS that evaluated pain, PGAP functional status assessment (FSA), and SF-36. The safety was performed by examined the values of SGOT, SGPT, BUN, and creatinine, to assess kidney and liver function at baseline, days 14, and 28.

Besides VAS, this study used PGAP functional status assessment (FSA) to demonstrates its reliability in the dimension of degree of dependence in performing basic activities of daily living. There are three dimensions of this measurement namely dependency, difficulty, and pain for 44 different activities of daily living (Table 1). Dependence score were assigned as follows: 0 = independent, 1 = uses mechanical assistance, 2 = uses human assistance, 3 = uses both mechanical and human assistance, and 4 = cannot perform the activity even with maximum assistance. Score for degree of difficulty and pain were assigned on a 4-point scale which range from 1 = no pain/ difficulty, 2 = mild pain/difficulty, 3 = moderate pain/ difficulty, and 4 = severe pain/difficulty respectively .

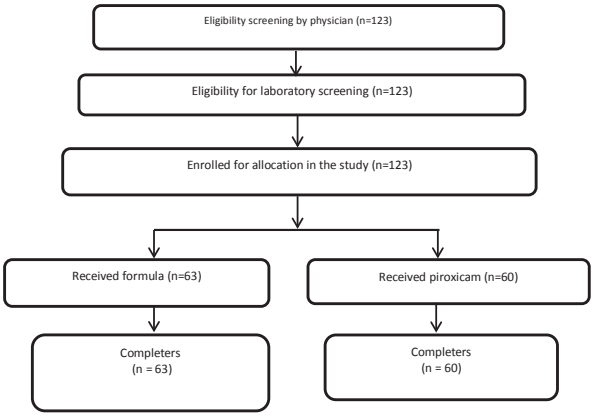

Figure 1. Flowchart of recruitment and enrollment process

Table 1. PGAP Functional Status Assessment (FSA) Instrument Items

Mobility	Personal Care	Work
Driving/Other transportation	Using a Telephon	Empoument/Ocupation
Shoping	Writing	Using Stove/Oven/Refrigerator
Walking Inside	Cutting Food	Using sink/faucets
Walking Outside	Drinking	Reaching Cupboards (High/Low)
Stairs in/to Home	Ability to wash all areas	Lifting Pots/Pans
Other Stairs	Turning Faucets	Peeling/ Cutting
Curbs	Care of Teeth	Opening containers
Transferring to/from bed	Shaving	Doing Laundry
Transferring to/from chair	Combing Hair	Sweeping/ Mopping
Transferring to/from toilet	Setting Hair	Cleaning Bathroom
Transferring to/from bath	Putting on and tying shoes	Washing Windows
	Putting on hose/pants	Doing home repairs
	Putting on shirt/blouse	Doing Yardwork
	Buttoning/ Zipping	Making beds
	Putting on sweater/coat	Washing dishes

Jamu formula

All subjects were instructed to boil 1L of water, and put jamu formula into boiling water, wait 15 minutes and stop the boiling process. Let the water cooling down, filtered and take it each a glass three times a day after breakfast, lunch, and dinner.

Statistical analysis

Data were analyzed statistically using a software proggrame for statistical analysis version 18.0. Descriptive data were calculated and presented as table to assess demographic characteristic, VAS, FSA, SF-36, and level of SGOT, SGPT, BUN, and creatinine between two groups.

RESULTS

A total of 123 subjects (patients) were randomly selected and administrated by jamu formula and piroxicam (17 male and 46 female in formula group, 19 male and 41 female in piroxicam group). The majority of patients are women, it shows that women have higher prevalence of OA than man at age of 50 years or more [9]. The result shows that jamu formula and piroxicam group were not significantly different ($p>0.05$) in demographic data e.g., sex, age, occupation, body mass index (BMI), and duration of OA (Table. 2).

Table 2. Comparison of formula and piroxicam groups in term of demographic

Characteristic	Formula group (n)	Piroxicam group (n)	Total (n)	P
Age				0,237[a]
50 – 60 y.o	17	25	42	
61 -70 y.o	46	35	81	
Sex				
Men	17	19	36	0.043[a]
Women	46	41	87	
Occupation				0.579 [a]
Retired	19	23	42	
Military/Police/Officer	9	11	20	
Employee	6	5	11	
Enterpreneur	16	11	27	
Labor/farmer/fisherman	4	5	9	
Other jobs	7	5	12	
BMT				
Underweight	2	2	4	
Normoweight	10	12	22	0.493[a]
Overweight	14	15	29	
Obes 1	32	25	57	
Obes 2	7	4	11	
Duration of OA	41.25 months	40.36 months		0.356[b]

([a]) Chi-square test; [(b)] paired t test

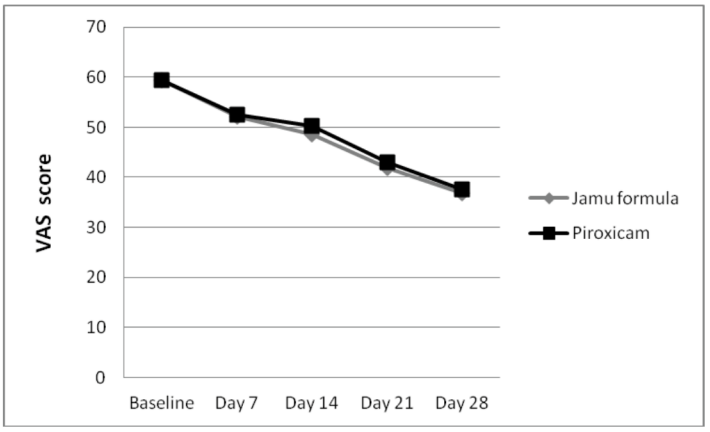

Figure 2. Comparison VAS score between formula and piroxicam group

This study was demonstrated the efficacy of the formula based on improvement of clinical parameters that were showed by VAS score, PGAP functional status assessment (FSA), and SF-36. VAS score that evaluated pain and stiffness, was assessed on the end of days 7, 14, 21, and 28. They were significantly different (p=0,000) if it was compared to their own VAS score on base-line. VAS score were decrease in both groups every time they were measured. To assess significantly VAS score between formula group and piroxicam group, was used *independent t-test* at the similar period. Mean baseline of both groups were not statistically significant (p=0,952) and the effect of formula and piroxicam on the end of days 7, 14, 21, and 28, were not statistically significant either (p>0.05) (Table. 3)

FSA score were measured on the end of day 7, 14, 21, and 28. The values of FSA were decreased gradually on formula and piroxicam group every measured. FSA score on the end of day 7, 14, 21, and 28, were significantly different (p<0,05) if it was compared to their own FSA score at baseline. To assess significantly FSA score between two groups, was used *independent t-test* at the similar period. Mean baseline of both groups were not statistically significant between them (p= 0,982). The jamu formula and piroxicam administration effects on FSA score statistically were not different (p>0,05) on the end of day 7, 14, 21, and 28 (Table 4).

Table 3. Comparison VAS score between formula and piroxicam group

VAS score	Formula group (Mean±SD)	Piroxicam group (Mean±SD)	p value
Baseline	59.44 ±10,.9	59.33 ±9.67	0.952; NS
Day 7	52.06 ±9.98	52.58 ±10.4	0.778; NS
Day 14	48.57 ±13.24	50.17 ±12.34	0.491; NS
Day 21	41.90 ±15.46	43.00 ±14.53	0.686; NS
Day 28	36.75 ±19.40	37.50 ±17.55	0.821; NS

Note: Statistical analysis was carried out using independent "t" test , p value p<0.05 (significant), NS = not significant

Table 4.Comparison FSA score between jamu formula and piroxicam group

FSA score	Formula group (Mean±SD)	Piroxicam group (Mean±SD)	p value
Baseline	9.82 ±1.57	9.35 ±1.53	0.982; NS
Day 7	8.62 ±1.91	8.25 ±6.9	0.892; NS
Day 14	8.38 ±1.83	7.77 ±1.67	0.461; NS
Day 21	7.14 ±1.76	6.83 ±1.68	0.911; NS
Day 28	5.72 ±1.40	5.51 ±1.22	0.780; NS

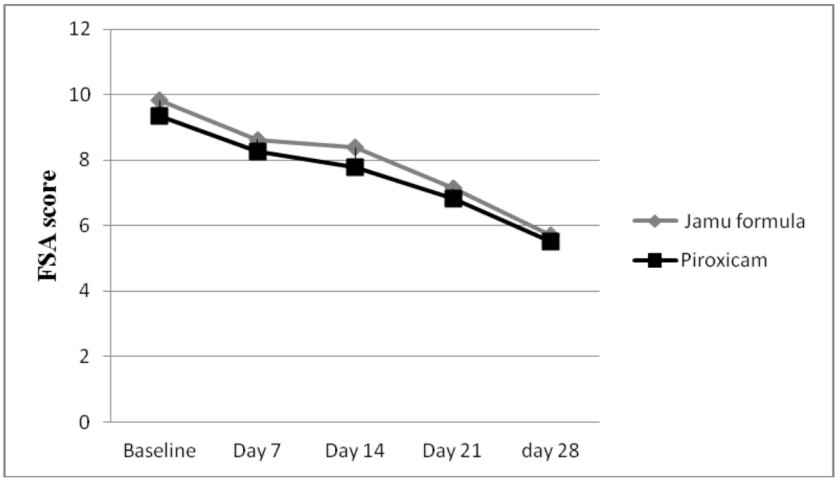

Figure 3. Comparison FSA score between formula and piroxicam group

The Short Form (SF)-36 is a generic measure which generated a profile of eight dimensions and for which there is some evidence for validity in OA patients [10]. Eight dimension of the SF-36 are physical functioning, social functioning, physical limitations, emotional limitation, pain, mental health, vitality, and general health perception. In this parameter, patients were measured only at baseline, day 14 and 28 (every two weeks) for generic and condition-specific outcomes. The statistical significantly of formula and piroxicam group in SF scores were assessed using paired T test, and it was significantly improved when compared to their baseline (Table 5). They were not statistically significant when compared between both of them on the similar period (p>0,05) except social functioning dimension on baseline (p=0,047) (Table 6).

To assess safety of the formula on liver and renal functions, the levels of the biological profiles were measured on baseline (pre-treatment) and day 28 (post-treatment). In biological parameters, SGPT, SGOT, BUN, and Creatinine level, showed normal range in both groups. There was no significant alteration in the levels of SGPT, SGOT, BUN, and Creatinine when compared with their own baseline (p>0.05) (Table 7). The statistical significantly of formula versus piroxicam group were assessed using independent T test, there was no significant differences (p>0,05) of the biological parameters when compared between them (Table 8).

DISCUSSION

A challenge osteoarthritis treatment is deciding which medications will provide the greatest symptom relief with lowest serious adverse effects[11]. Meanwhile, people who use of complementary and alternative medicine (CAM) belief that using"natural" treatments are safer than conventional medical treatments[12]. This study indicates the excellent efficacy and safety of the jamu formula and these promising OA symptoms relief result when compared with piroxicam as standart drug. Pain of the OA patient was significantly reduced after one week of formula intervention and much better after the end of intervention (day 28). The formula was found to be safe based on SGPT, SGOT, BUN, and creatinine level, showed in normal range.

Table 5. Comparison of SF-36 score on baseline, day 14, and day 28

Dimensions of SF-36	Formula group			Piroxicam group		
	Baseline	Day 14	Day 28	Baseline	Day 14	Day 28
Physical functioning	85.87±20.51	90.40±11.61*	91.90±11.62*	83.58±15.57	89.75±13.35*	91.04±12.55*
Social functioning	76.19±19.67	80.75±17.22*	83.73±17.33*	74.38±22.95	76.88±19.50*	81.88±18.62*
Role Limitations (physical)	74.60±39.01	88.89±23.67*	91.47±20.80*	74.58±37.53	91.04±24.26*	92.08±21.34*
Role Limitations (emotional)	82.01±35.83	93.65±21.67*	95.77±18.45*	84.44±32.16	92.22±23.26*	92.92±20.29*
Pain	66.19±23.40	76.63±20.59*	81.94±21.42*	63.83±20.64	72.88±18.80*	80.08±20.47*
Mental health	74.60±15.29	76.83±14.32*	79.87±14.37*	70.53±14.34	74.33±14.06*	74.93±16.55*
Vitality	71.47±18.20	75.95±15.13*	78.81±15.86*	71.33±15.15	75.42±13.06*	77.00±16.15*
General health perceptions	61.35±19.01	63.73±15.50*	72.93±12.69*	64.67±16.18	66.83±12.85*	71.67±12.71*

Note : Statistical analysis was carryout using paired t test, pvalue <0.05 (significant), (*) significant compared with their own baseline

Table 6. p values of SF-36 score between formula and piroxicam on similar period

Dimensions of SF-36	p values		
	Baseline	Day 14	Day 28
Physical functioning	0.318	0.835	0.616
Social functioning	0.047(*)	0.141	0.375
Role limitations (physical)	0.646	0.459	0.831
Role limitations (emotional)	0.352	0.498	0.143
Pain	0.354	0.431	0.733
Mental health	0.228	0.461	0.323
Vitality	0.163	0.178	0.465
General health perceptions	0.279	0.574	0.314

Note: Statistical analysis was carried out using independent t test, p<0.05 (significant), (*)significant

Table 7. Comparison of formula and piroxicam groups in term of biological parameters

Parameters	Formula (Mean±SD)			Piroxicam (Mean±SD)		
	Baseline	Day 28	p value*	Baseline	Day 28	p value*
SGOT	20.40±4.74	19.38±3.44	0.335; NS	20.77±4.61	20.88±4.70	0.344; NS
SGPT	20.75±4.71	19.94±4.23	0.267; NS	20.69±4.16	20.95±2.11	0.267; NS
BUN	24.06±5.79	23.96±5.86	0.145; NS	24.59±8.09	24.62±7.41	0.767; NS
Creatinine	0.876±0.27	0.817±0.27	0.328; NS	0.847±0.26	0.949±0.70	0.114; NS

Note: Statistical analysis was carried out using independent "t" test , p value p<0.05 (significant), (*) = significant

Table 8. P value of formula versus piroxicam group in term of biological parameters

Parameter	p value			
	SGOT	SGPT	BUN	Creatinine
Baseline	0.828; NS	0.404; NS	0.145; NS	0.691; NS
Day 28	0.260; NS	0.460; NS	0.288; NS	0.204; NS

Note: Statistical analysis was carried out using independent t test, p<0.05 (significant), NS= not significant

The primary compound of jamu formula is curcuma (Zingiberaceae), the most frequently used in Indonesian herbs formula. Zingiberaceae are generally safe for human consumption [13]. Curcumin is the major compound of *Curcuma domesticae* and *Curcuma xanthorriza.* Curcumin showed a significant improvement in morning stiffness, walking time and reduction in joint swelling [14]. Other compound of jamu formula is *Centella asiatica*, it contains flavonoid (quercetin, kaempherol, catechin, rutin, etc), triterpene (Asiatic acid, madecassic acid, asiaticoside, madecassoside), and essential oil (sesquoterpene,α-humule, trans β-farnesene, farnese, gemacrene-D, bicyclogermacrene, β-caryophelene, and p-cymol[15]. The bioactive compound of *Centella asiatica* showed antioxidant activity that could have potential in preventing or slowing the progress of inflammation [16] such as osteoarthritis.

Previous study indicated that an aerial part of *Orthosipon stamineus* from Indonesia, showed potent inhibitory activity against the NO production in lipopolysaccharide (LPS)-activated macrophages-like J774 cells [17]. Increased concentration of nitrate, indicating elevated NO production in synovial fluid and serum of the inflamed joints on rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis[18]. Various nonselective NO synthase inhibitors were used, such as orthosiphols A, B, D, X, H, K, M, and N, 7-O-deacetylorthosiphol B, 6- hydroxyorthosiphol B, 3-O-deacetylorthosiphol I, 2-O- deacetylorthosiphol J, neoorthosiphols A and B, norstaminol A, siphonols A–E, staminols A–D, orthosiphonone C and D, 14-deoxo-14-O-acetylorthosiphol Y, 2-O- deacetylorthosiphonone A, and neoorthosiphonone A[19].

Lignans are the important compounds in the *Phyllantus niruri* which have anti-inflammatory actions. Lignans seem to be directly or indirectly associated with their potency to inhibit ET-1 and to a lesser extent, PAF-mediated inflammatory responses [20]. In other compound, stem of *Equisetum debile* contains flavonoid, sterol, saponin and tannin. They are responsible to anti-inflammatory activities. The anti-inflammatory actions of *Equisetum debile*, can act centrally (such as narcotics) and peripherally (such as NSAIDs) but the exact mechanism remain in question [21].

Mechanism of herbal medicine for OA have not been clearly revealed, but interactions with inflammation mediators and reduce cartilage degradation maybe a rational approach to using herbal medicine[5]. This study used piroxicam for standard drug, because it is cheaper than other NSAIDs such as diclofenac and meloxicam. It widely used for OA pain in Indonesia. Piroxicam was used by patient just once a day, it increases compliance of patients. In other group, *Foeniculum vulgare* can increase compliances of the patients because of the fragrant. The fragrant can cover the bitter taste of formula. Study result showed there was a decrease of SGPT, SGOT, BUN, and creatinine level in jamu formula group, it shows nephro-protective [22,23,24] and hepato-protective [24,25] activities. Although, piroxicam group was an increased biological parameters but it still showed in normal range.

The knowledge of Jamu is part of the public health sector within the Indonesian health system. Jamu or herbal medicine in Indonesia has a important role in achieving a better equity of primary health care. Jamu

in the daily life of many Indonesians have been used mainly for self-medication. Traditional/herbal medicine has its own market, providing medication to some of the need of Indonesian people. Diversity, flexibility, easy accessibility, broad continuing acceptance, relative low cost, low levels of technological input, relative low side effects and growing economic importance are some of the positive features of Jamu.

In conclusion, the study found that osteoarthritis herb formula is effective and safe alternative for pain relief of OA and clinically comparable efficacy and safety to piroxicam after 28 days intervention.

Acknowledgments

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